Therapy with lamivudine and steroids in a patient with acute hepatitis B and rapidly progressive glomerulonephritis

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To the Editor: Tang *et al.*[1] recently reported that lamivudine (LAM) improves renal outcome in patients with chronic hepatitis B virus (HBV) infection and membranous nephropathy. We would like to add our experience on acute hepatitis B and rapidly progressive glomerulonephritis.

A 36-year-old woman, previously healthy and hepatitis B surface antigen (HBsAg) negative, presented in March 2005 with generalised oedema and macroscopic haematuria. Blood pressure was 160/90 mm Hg. Laboratory data (Table 1) showed high serum creatinine, massive proteinuria, and alanine aminotransferase higher than 30 u.n.l., with evidence of HBsAg, HBeAg, and HBV-DNA positive. Renal biopsy showed mesangioproliferative glomerulonephritis with crescents. HBsAg and HBcAg deposition in glomeruli was shown by immunofluorescence by monoclonal F(ab) antibodies (Figure 1a and b). LAM (100 mg/day) was started and alanine aminotransferase rapidly decreased, but renal function worsened. Ten days later steroid (methylprednisolone 500 mg/day intravenously for 3 days, then prednisone 1 mg/kg/day) was added. After 1 week, alanine aminotransferase fell at 137 IU/l, serum HBV-DNA dropped to 3.3×10^3 UI/ml, and renal function improved. The hypertension was treated with angiotensin-converting enzyme inhibitors, diuretics, and calcium antagonists. Four months later she underwent HBeAg seroconversion, HBV-DNA became undetectable by polymerase chain reaction and HBsAg was negative. Seven months after alanine aminotransferase normalised, proteinuria cleared, creatinine clearance rose to 82 ml/min and serum creatinine was normal (Table 1). Steroids were stopped, while LAM was continued for 3 months after HBsAg seroconversion.

Our report confirms the direct association between HBV infection and development of nephropathy[2] and supports the efficacy and safety of LAM in patients with HBV-related nephropathy.[1,3] LAM, through its rapid and potent antiviral action, allows immunosuppression to be performed effectively without any undue effect on HBV replication or risk of chronicity of infection.

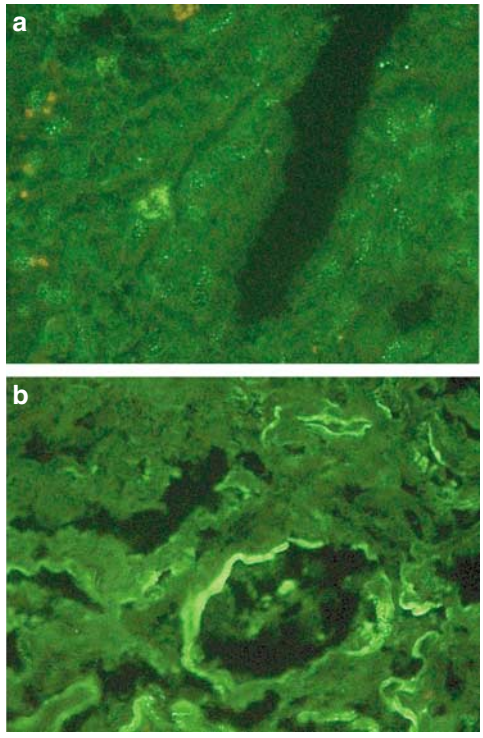

Figure 1 | (a) HBcAg expressed as coarse granules in the nuclei of most cells of the proximal renal tubules. One cell displays cytoplasmic clumps of HBcAg. (**b**) HBsAg deposited in crescents in a glomerulus and on the luminal border of some tubules.

Table 1 | Laboratory data

	23 March 2005	2 April 2005	9 April 2005	20 June 2005	25 July 2005	16 October 2005
Therapy	LAM	LAM+steroids	LAM+steroids	LAM+steroids	LAM+steroids	LAM
BUN (mg/dl)	128	182	192	82	42	43
Creatinine (mg/dl)	3.8	7.1	3.3	1.5	1.2	1.1
Creatinine clearance (ml/min)	14	6	18	61	60	82
Albumin (g/dl)	2	3.8	4	4.4	4	4.7
Proteinuria (g/24 h)	12	8.5	8			0.08
ALT (u.n.l. 31 IU/l)	900	331	137	259	40	23
Bilirubin (g/dl)	0.5	0.7	0.5	0.3	0.3	0.2
HBsAg/anti-HBs	+/−	+/−	+/−	−/−	−/−	−/+
HBeAg/anti-HBe	+/−	+/−	+/−	−/−	−/+	−/+
Anti-HBc IgM (Imx units)	2.48		1.47	0.4		0.2
HBV-DNA (UI/ml)	2.8×10^6	1.2×10^4	3.3×10^3	$<2 \times 10^2$	$<2 \times 10^2$	$<2 \times 10^2$

ALT, alanine aminotransferase; HBsAg, hepatitis B surface antigen; HBV, hepatitis B virus; LAM, lamivudine.

1. Tang S, Lai FM, Lui YH *et al.* Lamivudine in hepatitis B associated membranous nephropathy. *Kidney Int* 2005; **68**: 1750–1758.
2. Bhimma R, Coovadia HM. Hepatitis B virus-associated nephropathy. *Am J Nephrol* 2004; **24**: 198–211.
3. Connor F, Rosenberg A, Kennedy S *et al.* HBV associated nephrotic syndrome: resolution with oral lamivudine. *Arch Dis Child* 2003; **88**: 446–449.

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Is i.v. iron really superior in CKD patients not on dialysis?

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To the Editor: Van Wyck *et al.*[1] administered 1 g intravenous (i.v.) iron over the first 2 weeks, whereas oral iron was given over 8 weeks. As the rates of administration of iron were different, the appropriate comparison should be the proportion of patients achieving the primary end point at the end of 10–12 weeks and make the results more clinically relevant. In the analysis presented, it is assumed that patients who achieved 1 g/dl increase in hemoglobin at 2 weeks would also have the same response at 56 days. In the interest of intention-to-treat, the authors should also present the data for all patients randomized even when erythropoietin dose was not stable at baseline. The authors should be cautious in concluding that i.v. iron is safe in the long term. Progression of chronic kidney disease takes years and it would appear naive to declare safety of i.v. iron by reporting two estimated glomerular filtration rates over a course of 56 days! Notably, the improvement in hemoglobin with i.v. iron was only 0.3 g/dl more in the i.v. iron group, and 2/30 patients who received the high dose of 500 mg iron sucrose experienced severe hypotension sufficient to visit the emergency room. Thus, caution is warranted, when using high-dose i.v. iron. The authors measured C-reactive protein, yet do not report the data. Change in proteinuria was not reported and the multivariate logistic model for odds of hemoglobin response was also not presented as stated in the methods. These additional data would help interpret the results of this trial better.

1. Van Wyck DB, Roppolo M, Martinez CO *et al.* A randomized, controlled trial comparing IV iron sucrose to oral iron in anemic patients with nondialysis-dependent CKD. *Kidney Int* 2005; **68**: 2846–2856.

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Response to Is i.v. iron really superior in CKD patients not on dialysis?

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Dr Agarwal[1] raises a number of important questions. The answer to the title question would seem to be yes, i.v. iron is superior to oral iron. Moreover, the degree of difference is clinically significant: in chronic kidney disease patients with anemia (hemoglobin (Hb) <11 g/dl) without erythropoiesis-stimulating agents (ESA) or without an increase in ESA dose, i.v. iron administration will raise the Hb higher, stimulate a Hb increase >1.0 g/dl more often, achieve or exceed the target Hb threshold of $\geqslant 11.0$ g/dl more consistently, and replete iron stores more reliably than oral iron therapy. The answer to whether we should have included patients with ESA dose increases in the analysis of efficacy is no. Increasing ESA doses, like starting ESA anew, administering additional i.v. iron off protocol, or transfusing the patient, introduces a co-intervention. The penalty for including co-interventions is the inability to isolate iron treatment effects. As we discussed, previous randomized controlled trials that failed to preclude co-interventions failed to show between-group differences in patients assigned to i.v. iron or oral iron treatment.[2,3]

Was the duration of the trial sufficient to show efficacy? We demonstrated that the peak Hb response in both treatment groups occurred before 42 days, well before completion of the 56-day observation period. Among patients assigned to oral iron, peak increase in Hb was lower than in i.v.-treated patients, as we showed, but time to peak increase did not differ between groups (Cox proportional hazards model: 36.1 vs 39.9 days, oral vs i.v.; $P=0.3481$). Logistic regression analysis yielded only baseline ferritin <100 ng/ml as a significant covariate in increasing the odds of a positive Hb response, a result we explored in more detail in the analyses we presented in Table 2.

Was the duration of the trial sufficient to conclude that i.v. iron, compared to oral iron, is safe in patients with chronic kidney disease? Three randomized controlled trials, including ours, have examined the effect of i.v. iron administration compared to oral iron therapy on renal function in chronic kidney disease patients. In the first, patients given i.v. iron sucrose 300 mg monthly up to 6 months showed a rate of decline of renal function no different from that seen in patients given oral iron.[2] In the second, patients assigned to oral iron therapy showed a significant decline in ClCr, whereas their counterparts given i.v. iron dextran 100 mg twice monthly up to 3 months showed no decline.[4] Our results in patients who received five 200 mg doses or two 500 mg doses of iron sucrose showed a slower rate of decline of glomerular